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## CURRENT Trends AND New Developments in HIV research and Periodontal Diseases

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### Abstract

With the advent of combined antiretroviral therapies (cART), the face of HIV infection has changed dramatically from a disease with almost certain mortality from serious comorbidities, to a manageable chronic condition with an extended lifespan. In this paper we present the more recent investigations into the epidemiology, microbiology, and pathogenesis of periodontal diseases in patients with HIV, and the effects of cART on the incidence and progression of these diseases both in adults and perinatally infected children. In addition, comparisons and potential interactions between the HIV-associated microbiome, host responses and pathogenesis in the oral cavity with the gastrointestinal tract and other areas of the body are presented. In addition, the effects HIV and cART on comorbidities such as hyposalivation, dementia, and osteoporosis on periodontal disease progression are discussed.

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Over the past 40 years the prognosis of human immunodeficiency virus (HIV) disease has changed dramatically. What was once a disease with a high mortality rate preceded by dramatic declines in immune function accompanied with variety of life altering morbidities, has become a manageable chronic condition. This change in the prognosis of the disease is due in large part to the advent and continued improvements in combination antiretroviral therapy (cART). However, despite the many successful outcomes of cART, new challenges associated with its possible detrimental side-effects have arisen. Furthermore, additional complications inherent to the aging of the population living with HIV infection also need to be addressed. Globally in 2017, there were approximately 36.9 million people living with HIV at the end of 2017 with 1.8 million people becoming newly infected (<http://www.who.int/news-room/fact-sheets/detail/hiv-aids>). However in developed countries such as the United States, the demographics of HIV infected individuals have shifted with more than half the population with HIV being currently over the age of 50 years.<sup>1</sup> For the dental practitioner treating these individuals, there is an increasing need to address the common age related dental diseases such as periodontal disease. Furthermore, these older individuals may present with other co-morbidities associated with HIV infection, the antiretroviral treatment, or a combination of both, that could contribute to a higher incidence and severity of periodontal disease.

In addition to the challenge inherent to a population of aging HIV patients, there remain challenges on the opposite end of the demographic spectrum with children and adolescents who were infected either at birth or early childhood due to maternal exposure. These HIV infected children/adolescents, most of whom became infected perinatally prior to routine HIV-testing of pregnant women in the US before the early 2000s, may also develop HIV and ART related co-morbidities including periodontal disease as they enter adulthood.

In addition to these changing epidemiologic trends in HIV infection in the United States and in other developed and developing countries, there remain many unanswered questions for dental research: These include: 1. What are the underlying mechanisms and relationships between HIV and cART and their effects on the oral microbiome and immune milieu in the development of oral and systemic pathology?; 2. What new insights can be gained in periodontal disease progression from recent laboratory and clinical studies in HIV-infected patients which compare and contrast the microbiology, immunology, and inflammatory host response between connected areas of the body such as the oral cavity and periodontium to the gut and blood circulation?

In this paper, we will review the current scientific literature pertaining to changes in the epidemiology and microbiology of periodontal disease in populations with HIV disease in the era of cART. In addition, there has been a more recent focus on the interactions between periodontal diseases and systemic conditions and co-morbidities associated with HIV infection. These more recent investigations have brought together research and clinical disciplines that have focused on the mouth and periodontal disease with disciplines that have focused on other areas of the body such as the GI tract, brain, and vagina. These interactions and comparisons between oral and systemic health are explored in this review.

## **RECENT TRENDS IN THE EPIDEMIOLOGY OF PERIODONTAL DISEASE IN POPULATIONS WITH HIV DISEASE**

Before the advent of cART, atypical lesions involving the periodontal tissues were observed including linear gingival erythema (Figure 1) and a range of necrotizing periodontal diseases either restricted to the gingiva per se (e.g. necrotizing ulcerative gingivitis), or extending further into the periodontium to involve the soft tissue attachment and alveolar bone (e.g. necrotizing ulcerative periodontitis (Figure 2))<sup>2</sup>. Similar lesions involving the adjacent hard and soft tissues of the mandible, maxilla, hard palate and buccal vestibule (necrotizing stomatitis) were also described (Figure 3). It has been hypothesized that necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis, and necrotizing stomatitis each represent a different stage of the same disease<sup>3-5</sup> and may reflect the overall systemic progression of HIV infection to more severe collapse of the immune system and progression to full blown AIDS<sup>6-9</sup>. However, with the advent of cART a marked decline in the frequency of destructive periodontal disease in HIV patients has been reported. The frequency of these conditions continue to be higher in developing countries due to a lack of access to the most effective cART regimen and to dental hygiene and care<sup>10-12</sup>.

Nevertheless, with the increase in the average age of the general HIV population in the United States, other developed countries, and some developing countries, attention has now

turned to two areas of periodontal research: First is the incidence, severity and management of the more common chronic periodontal diseases in the aging adult population, where age is a major risk indicator as seen in non-HIV infected individuals<sup>13</sup>. Second is the incidence and progression of periodontal disease in the population of children and adolescents who acquired the HIV perinatally.

Epidemiological studies on the most common form of periodontal disease in the older population, previously termed “chronic periodontitis”, have and continue to show a range of possible associations between HIV and the incidence and severity of periodontal diseases. Before the advent of ART, some studies reported a greater attachment loss in HIV patients with preexisting chronic periodontal disease when compared to non-infected patients which correlated with declining CD4 counts<sup>14–18, 19</sup> and a greater extent of gingival recession with or without greater alveolar bone loss<sup>20, 21</sup>.

In the cART era, studies have reported reductions in oral candidiasis and hairy leukoplakia<sup>9,22–27</sup>, and a decrease the prevalence of periodontal diseases in HIV adults<sup>28</sup>. In addition, the cART era studies that compare the incidence and severity of periodontal disease between HIV infected patients receiving cART and non-HIV patients have shown no significant differences between these two groups<sup>21,22,29,30</sup>. Furthermore, in a large longitudinal study conducted from 1995 to 2002 on a female cohort, no significant differences were found in baseline mean clinical attachment levels and probing depths or progression of attachment loss and pocket depths between HIV positive and HIV negative women<sup>31</sup>.

One area of continued investigation is the finding that while there may be no increase in clinical attachment loss in HIV infected vs non infected patients with chronic periodontitis, there has been a reported increase in gingival recession in HIV patients<sup>20</sup>. One possible explanation is that the HIV patient may share some local microbial or destructive inflammatory characteristics with the necrotic periodontal lesions seen more commonly in the pre-cART era<sup>32,33</sup>. Furthermore, it is still possible the characteristics of the local microbiome, virome and mycobiome of the chronic periodontitis lesion in the aging HIV patient may share some of the same patterns as seen in the destructive periodontal lesions in the pre-cART era. Recent finding of these possible unique microbial signatures persistent in the cART era as well as their implications for the pathogenesis of periodontal disease will be discussed in the next section.

In the cART era, as in the pre cART era correlations between CD4 and/or HIV viral load with periodontal attachment loss or pocket depth have been inconclusive with some studies reporting no major differences in other periodontal parameters between HIV infected and non-infected patients<sup>34</sup> or in tooth loss patterns<sup>35</sup> particularly for patients with CD4 counts 500<sup>36</sup>. By contrast patients under cART who may have either developed a resistance to cART or lack of compliance to therapy and who experienced a 10-fold increase in viral load did show a marginal increase in tooth loss<sup>31</sup> while another study reported that patients under cART but with CD4 count <200 cells/mm<sup>3</sup> were at greater risk for periodontal disease<sup>7</sup>. These observations point to the need for earlier initiation, continuation, and patient compliance to cART as this approach may decrease the risk of marked immunosuppression

in HIV which may in turn reduce the incidence, severity and progression of periodontal disease.

As discussed previously, while one focus of periodontal research in HIV has shifted to the aging population undergoing cART a second focus on periodontal disease has shifted towards studies on children<sup>37</sup>. While some of these studies have focused on the less common prepubertal aggressive forms of periodontitis, other studies have focused on the more common periodontal changes in gingival health per se in children and adolescents that would normally precede manifestations of more advanced periodontal disease. These clinical changes include gingivitis and early indications of periodontitis, including increased pocket depths and the subtle clinical signs of attachment loss. Early studies of children in the USA in the pre cART era using clinical parameters of bleeding on probing, increases in probing depths and or loss of clinical attachment, reported a range of the incidence of gingivitis and early periodontitis from 55% to 94%<sup>38</sup>. A similar wide range of gingivitis using a range of diagnostic criteria including bleeding on probing and visual clinical inflammation was reported in other countries. For example there have been reported rates of gingivitis at 49% in Romania<sup>39</sup>, 13.5 to 17.5% in Brazil<sup>40,41</sup> 2.2% in Thailand<sup>42,43</sup> and 10.8% in India<sup>44</sup>. More recently in the cART era, several large scale cross sectional and prospective epidemiological studies have been conducted to examine the effects of these treatments on the incidence and severity of periodontal diseases in children and adolescents. One large multicenter prospective cohort study of 2767 HIV infected children at sites in the United States and Puerto Rico reported a much lower incidence of herpes zoster and oral candidiasis (Figure 4) in children on cART when compared to those in the pre-cART era<sup>45</sup>.

One advantage of studying periodontal diseases in perinatally exposed children as they progress through childhood, adolescence, and adulthood is that comparisons in disease progression can be made between HIV infected children and other children in the similar environment and socioeconomic who are not HIV infected. Such studies are much less affected by the potential multiple environmental and behavioral differences that often make it difficult to determine the effects of HIV infection itself on the incidence and progression as well as the underlying microbiological, immunological, inflammatory, genetic, and other considerations for the progression of periodontal disease. Recently a multicenter study was undertaken in the United States to assess the effects of HIV on periodontal diseases and other oral diseases and conditions by comparing children and adolescents perinatally exposed and infected with HIV (PHIV) with perinatally HIV exposed but uninfected (PHEU) children (PHACS-AMP Oral Health Substudy). The majority of these study participants shared similar socioeconomic status. In this baseline AMP Oral Health Substudy, the prevalence of periodontal disease did not differ between PHIV and PHEU with 32% of this youth population having mild/moderate periodontitis as defined by the modified CDC classification system. However, using this same classification system, this prevalence was higher than the 22% reported in the Nutrition Examination Survey (NHANES) survey of an older general population of 30–34 year-old subjects<sup>46,47</sup>. Among PHIV youth, younger age of first exposure to cART was associated with fewer number of teeth with multiple sites of bleeding on probing.<sup>48</sup> A current follow-up study on this HIV infected and HIV exposed uninfected cohort is currently underway to assess and compare the periodontal health of these cohorts as they progress to young adulthood.

## CURRENT AND NEW INVESTIGATIONS INTO THE MICROBIOLOGY AND THE HOST RESPONSE IN PERIODONTITIS IN THE HIV PATIENT

In the pre cART era, the vast majority of microbiological studies on periodontal diseases in HIV and non-HIV infected patients focused on the bacterial profiles or microbiome of both the atypical necrotic periodontal lesions and linear gingival erythema as well as more common acute and chronic periodontal diseases<sup>49,50</sup>. The atypical lesions of the pre cART era were characterized by a diffuse invasion from viruses, fungi, and other opportunistic organisms into the gingival tissue and underlying periodontal support from both the tooth surface and soft tissue surface, with a reduction of cells of the local innate and acquired immune system<sup>51–61</sup>. This is in contrast to chronic periodontal diseases in HIV uninfected individuals where inflammatory cells are localized primarily to the connective tissue regions under the junctional and sulcular epithelium adjacent to the supra and subgingival biofilm on the tooth surface<sup>50</sup>.

The advent of cART has provided the opportunity to make comparisons between HIV-infected patients and non-infected patients, and within HIV patients before and after cART for the more common forms of periodontal diseases. In addition, and equally important, newer avenues of research have turned their attention to not only the microbiome, but also other viruses (the virome) and fungi (the mycobiome) associated with HIV and the interactions between all of these three populations of the microbiome with each other. In addition, there are new investigations and insights into the interactions of this complex microbiome with immunological and inflammatory responses and with the effectiveness of cART. In this section, these trends in changes in the microbiology of HIV, in the periodontium and in other oral and systemic sites, will be presented for each of these microbiome, virome and mycobiome populations with newly discovered interactions and clinical implications.

### The Microbiome in HIV in the cART Era

In the pre cART era, with the greater prevalence of the less common HIV associated lesions and conditions of the periodontium such as linear gingival erythema, necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis, as well as conventional periodontal diseases such as chronic periodontitis, each of these conditions may have presented alone or in combination of these lesions and conditions. Earlier studies demonstrated that the bacterial microbiome profile of each of these conditions was characterized by species normally associated with periodontal diseases as well as unique opportunistic flora that may present in the more destructive and/or necrotic lesions. For example, the similarities in the microbiome between linear gingival erythema and necrotizing ulcerative periodontitis in HIV patients implied that there was a continuum between these lesions<sup>62–67</sup>.

For conventional chronic periodontitis most studies demonstrated that the microbiome was similar between HIV positive and HIV negative patients, with the exception of several opportunistic microorganisms. In addition certain combinations of suspected periodontal pathogens are more prevalent in the HIV positive patient<sup>68</sup>. In particular the higher detection rates of a variety of treponemes (spirochetes) in HIV patients may have clinical

significance as they have an important role in the pathogenesis of chronic periodontal diseases and necrotizing periodontal diseases<sup>69,70</sup>. In the cART era, different microbiome studies have reported both similarities and differences between HIV patients with cART and non-infected HIV patients. For example, some studies have demonstrated no differences in microbiota between HIV infected cART patients and non HIV infected patients<sup>71</sup> while other studies have shown marked differences<sup>72-76</sup>. For example, in patients on cART, *Enterococcus faecalis* and *Fusobacterium nucleatum* were observed in higher numbers inversely related to lower CD4 counts<sup>77,78</sup>. More recent microbial studies in the cART era mirror the previous findings for the pre-cART era in that in general there are no major differences in the periodontal microflora in chronic periodontitis between HIV positive and negative patients, particularly for the classic periodontal pathogens<sup>79</sup>. However, in the cART era there continue to be reports of atypical/opportunistic microbial species isolated from the periodontal pockets of HIV patients<sup>80</sup>. For example, some recent reports have demonstrated that in HIV patients, opportunistic pathogens such as *Helicobacter pylori*, *E. faecalis* and *Pseudomonas aeruginosa*<sup>81</sup> are still detected in higher frequency in the subgingival biofilm.

For longitudinal studies of the periodontal microbiome in the cART era, several recent studies have taken advantage of the opportunity to examine changes in the microbiome in the individual patient before and after cART. Some of these studies have found differences in the microbiome with cART before and after treatment<sup>74,75</sup>. For example, in the Women's Interagency HIV study which specifically examined species with pathogenic potential in periodontitis, cART use increased the risk of recovering pathogenic bacteria such as *Fusobacterium* species, enteric gram-negative rods, *Peptostreptococcus micros*, *Campylobacter* species, *Eubacterium* species, and *Tannerella forsythia*<sup>72</sup>. In addition, several studies have shown that cART may reduce the counts of commensal bacteria which have a protective effect on the colonization of pathogenic species<sup>72,74,75</sup>.

The oral microbiome in children with HIV is an area that has been the focus of several recent studies. Children infected with HIV from their mother perinatally present a unique opportunity to study the development of the oral microbiome. Most of these earlier studies on infants were performed in developing countries in Africa, with some recent studies performed in the United States<sup>82-84</sup>. From the time of birth to their later development, children acquire their initial oral microbiome from their mother, and their early environment plays a major role in the development and maturation of the oral microbiome under the influence of HIV and cART. In addition, there is an opportunity to compare the development of this oral microbiome with those children/youth under similar beneficial or detrimental environmental conditions<sup>85</sup>. For example, in the recent PHACS-AMP cross sectional multicenter study on HIV and oral health in both PHIV and PHEU youth, no significant differences in the oral microbiome were noted with some exceptions, such as lower levels of *Corynebacterium* and *Streptococcus mutans* among PHIV youth. As *Corynebacterium* is considered one of the health-associated taxa in plaque, this may be one possible contributing factor in the higher caries prevalence in HIV infected youth observed in one study<sup>86</sup>. In addition, follow-up studies of these types of cohorts may yield new insights into changes in the microbiome associated with changes in periodontal health.

There is considerable evidence that alterations in the oral microbiome as a result of cART may have impact on a range of local and systemic diseases and conditions. The pathogenic properties of this altered microbiome can produce products that stimulate the local inflammatory and immune response and release of inflammatory cytokines and chemokines, which contribute to the initiation and progression of periodontal diseases<sup>87</sup>. In addition, with this emerging evidence that cART may alter the composition of the oral microbiome, two other important interrelationships between the effectiveness of cART and the oral microbiome have been proposed. The first is determining if there are differences in the microbial diversity in saliva from persistent high HIV viral load and low CD4 to patients with HIV patients normal CD4 count and minimal to no viral load as another approach to assess the effectiveness of cART<sup>75</sup>. The second are the recent observations that alterations of the microbiome in the vagina have the potential to metabolize cART drugs<sup>88</sup> and thereby reduce their clinical effectiveness. The possible effects of the oral microbiome in metabolizing cART drugs has yet to be explored. The implications of each of these proposed interrelationships merits further investigation.

### The Virome in the cART Era

In the HIV infected patient the role of other oral non-HIV viruses in the initiation and progression of both the necrotic periodontal conditions more commonly reported in the pre cART era, as well as more common chronic periodontal diseases that are frequently detected in the cART era has been extensively studied. In HIV infected patients, a full range of viruses including cytomegalovirus<sup>89</sup>, herpes zoster<sup>90</sup> and human papilloma virus<sup>91</sup> have been isolated from both necrotic periodontitis as well as chronic periodontitis. In particular for chronic periodontitis, viruses in the herpesvirus family which include cytomegalovirus, Epstein-Barr virus, and herpes simplex virus 1 and 2 have also been detected in periodontal pockets of HIV infected patients, and are found in higher numbers when compared to HIV non-infected patients<sup>92,93</sup>. More recent research on Epstein-Barr virus have shown that they are present in both chronic and aggressive forms of periodontal diseases<sup>94,95</sup>, and that they, along with other herpesviruses, are shed into the oral cavity at a greater rate with more severe immunosuppression<sup>96</sup>.

Several mechanisms for the direct and indirect role of these viruses in the initiation and pathogenesis of periodontal diseases have been proposed. These include the role of these viruses in promoting the overgrowth of periodontal pathogens and opportunistic infections by suppressing both innate and acquired immunity to pathogenic bacteria, and by directly or indirectly promoting the production and release of a range of inflammatory mediators that result in destruction of the periodontal support.<sup>97</sup> Insights into the interactions between herpesviruses and the microbiome and host response and implications for periodontal disease progression are presented in more detail in the paper by Chen et al. (add to the reference list) in this volume.

With the advent of cART it would appear that detection levels of these non-HIV viruses would be lower than in the pre-cART level. While these declining trends have been reported for many classes of viral species, detection of oral human papilloma virus and their clinical manifestations in the oral cavity (Figures 5 and 6) have remained essentially the same<sup>98</sup>.

Control of human papilloma virus presents a unique challenge to the health practitioner as there is a strong association of the presence of human papilloma virus with oral pharyngeal carcinomas<sup>99</sup>. In several studies conducted in the cART era, the detection rates of oral human papilloma virus has been ranging from 14 to 37% of HIV-infected persons compared to less than 10% of non-HIV infected persons<sup>100–103</sup>. In addition, indirect evidence for the association of cART and persistence of human papilloma virus has been demonstrated in the recent PHACS (Pediatric HIV and AIDS Cohort study), where human papilloma virus infection was associated with lower nadir CD4 levels<sup>104</sup>. Therefore, as in studies of the bacterial microbiome, the direct or indirect effects of cART in altering the viral microbiome may have both beneficial and detrimental effects.

### The Mycobiome in the cART Era

Oral candidiasis is a common clinical manifestation of immunosuppression due to HIV infection (Figure 4). In addition, the role of candida and possible other yeasts in the pathology of the atypical periodontal lesions as well as in more common periodontal conditions has received considerable attention since the beginning of HIV research. Candida species have been detected in high numbers in the plaque biofilm of HIV positive patients<sup>16,33,69,105–108</sup>. As with viruses, candida and other yeasts may also play a role in the progression of these necrotic lesions into the supporting alveolar bone. In the pre-cART era, the invasion of candida into the periodontal soft tissues appeared to be directly connected with the occurrence of atypical periodontal lesions including linear gingival erythema, and necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis<sup>33,108,109</sup>. As with periodontal bacterial pathogens and viruses, the presence of candida in the periodontal pocket and/or invasion of candida into the periodontal tissues may trigger a destructive inflammatory response<sup>108,110,111</sup> leading to tissue necrosis seen more commonly in the pre-cART era. In addition, this candida induced inflammatory response may promote loss of clinical attachment and resorption of alveolar bone in chronic or aggressive periodontal diseases in the HIV positive patient. This destructive inflammatory effect induced by candida and other yeasts could include the release of potentially destructive enzymes to periodontal tissue from adjacent “primed” neutrophils attempting to neutralize this candida invasion<sup>111</sup>. In addition to a “primed” neutrophil response, priming of other inflammatory responses to HIV may play a role in the pathogenesis of periodontal disease<sup>8</sup>. These include excessive production of interferon-gamma<sup>87,112</sup>, prostaglandins<sup>113</sup>, matrix metalloproteinase-9, tissue inhibitors of metalloproteinases-1, and other metalloproteinases<sup>57,58</sup>, interleukin-1 $\beta$ , interleukin-6<sup>114</sup>, transforming growth factor-beta<sup>115</sup>, and interleukin-2 and interleukin-18<sup>87</sup>. As in HIV uninfected patients, several of these inflammatory cytokines are found in higher concentrations in deeper vs. shallower pockets<sup>53–55,116</sup>. This elevated inflammatory cytokine response in HIV infected patients may be in response in part to the HIV infection per se, and/or opportunistic infections such as candida. This primed inflammatory response may in turn play a role in the pathogenesis of chronic periodontitis in HIV subjects<sup>112</sup>. These patterns of tissue destruction in the HIV infected patient would occur both within the gingival crevice and within the oral gingival epithelium.

In the past, the focus of the effects of candida on periodontal disease have centered on these destructive inflammatory effects. However, more recent research has also indicated that



candida itself may have protective effects against HIV. This recent novel finding was proposed in studies that observed that increased vaginal candidiasis is associated with reduced levels of HIV particles <sup>117</sup>. In contrast to the role of periodontal bacterial pathogens in promoting the adherence, invasion and activation of HIV particles, candida may exhibit these protective effects against HIV through the stimulation of the production of anti-HIV chemokines including RANTES and Interferon alpha beta, by sequestering HIV particles, and by inhibiting the binding of HIV to target cells. <sup>118</sup>. Therefore, the balance between the protective and destructive effects of candida in HIV infection and implications for periodontal and oral health merit further investigation.

## **MICROBIOLOGY AND PATHOGENESIS OF HIV IN THE ORAL CAVITY AND GUT: SIMILARITIES, DIFFERENCES AND INTERACTIONS**

In the non-HIV infected patient with periodontal disease, there is now a large body of evidence demonstrating the ability of oral bacteria and their toxic by-products to translocate across the mucous membrane resulting in systemic diseases. Infective endocarditis is the most well-known of these, specifically after dental procedures. Other systemic diseases associated with periodontal disease are diabetes, rheumatoid arthritis and premature delivery which are likely due to the toxic by-products and bacterial translocation from the oral cavity, which then induce chronic systemic inflammation. The presence of an HIV infection adds a third component that can play into these oral and systemic interactions. When considering the interactions between HIV and the oral and gut microbiome, there are three areas of investigation that have received considerable attention. The first area of investigation centers on the ability of HIV to attach and invade the surface epithelium and underlying tissues of the oral cavity and gut. The second area of investigation centers on the effects of HIV on altering the microbiome of the oral cavity and gut and promoting the translocation of other bacteria, fungi, and viruses into the bloodstream to other sites of the body. The third area of investigation centers on the role of the microbiome of the oral cavity and gut in activating latent HIV reservoirs. For each of these three areas of investigation, the gut and oral cavity share some similarities as well as some important differences which are discussed in this section.

When assessing the potential of HIV to attach to the surface of the oral cavity or gut and invade deeper tissues, one important question arises: Why is the gut more susceptible to attachment and invasion of HIV, while the mouth in general is more resistant to HIV invasion? This difference may be due in part to differences in the type and magnitude of host defenses in these two areas of the oral/gastrointestinal tract. In addition, in health, the oral mucosa normally expresses low levels of CCR5 which may account for the low binding affinity of the HIV virus to the oral epithelium <sup>119</sup>. While studies on periodontal diseases have shown that there is an increase in surface HIV primary receptors (glycoprotein [gp]120) and co-receptors (such as CCR5) in gingival epithelium which would promote HIV attachment and invasion of target cells, this is offset by a significant local increase in antiviral alpha and beta defensins of the innate immune system <sup>119,120</sup>. These observations may help explain why there is a lack of direct evidence of invasion of HIV in the oral cavity in periodontally healthy and periodontally diseased patients <sup>119</sup>.

For the actual translocation of bacteria, fungi, and non-HIV viruses into the bloodstream, both the oral cavity in general, the inflamed periodontal pocket in particular, and the lining of the gut mucosa are potential sites for bacteria to cross a damaged or compromised protective epithelial barrier and enter the blood stream where they may have detrimental effects on other organ systems and other locations in the body. This process of bacterial translocation has been proposed as a central mechanism for the possible periodontal-systemic connection in the field of periodontal medicine. As previously discussed, while the role of HIV itself in promoting this translocation through the inflamed periodontal pocket has not been investigated, there is a considerable body of evidence from research on the gut that HIV itself may affect the composition of the gut microbiome, which in turn would affect the permeability of the protective gut mucosa, thereby leading to translocation of gut bacteria into the bloodstream<sup>121,122</sup>. Furthermore, in patients with cART there is residual chronic inflammation as well as residual elevation of opportunistic bacteria, and decreases in beneficial bacteria both in the gut and in the oral cavity<sup>76,123</sup>. This persistent inflammation and presence of a more pathological microbiome can also lead to dysfunction of the mucosal barrier and translocation of the microbiome. The resulting persistent local and systemic inflammation and bacterial translocation can in turn result in the co-morbidities associated with HIV infection in patients with cART. It is well established that when the gingival epithelial barrier is damaged or when there are inflammatory changes in the underlying periodontal tissues, bacterial translocation can occur leading to systemic bacteremia<sup>124</sup>. In particular, HIV protease inhibitors used as part of the cART regimen have been of interest because of their known mechanism of action and undesired side effects. For example Danaher et al<sup>125</sup> showed that certain protease inhibitors can block oral epithelial cell DNA synthesis, which causes a reduction in healing and potential microbial shifts and destruction of the mucosal barrier, thereby enhancing translocation.

One other mechanism that has been shown to promote the translocation of bacteria through the gut lining but as of yet not in the oral cavity, is the effect of HIV on depletion of TH-17 cells<sup>126,127</sup>. In the oral cavity, the presence of high numbers of TH17 cells are associated with higher levels of secretion of the pro inflammatory cytokine interleukin-17. However, as with the prostaglandins, at lower concentrations this cytokine is also required to maintain mucosal integrity in the gut<sup>128</sup>. Thus, depletion of interleukin-17 may therefore further promote bacterial translocation<sup>129</sup>. Furthermore, this relationship between the gut microbiota and HIV infection has been shown to be reciprocal in that alterations in the gut microbiota can in turn promote the attachment of HIV to the gut mucosa as well as to cells of the immune system which are the primary target of the HIV<sup>130,131</sup>.

Perhaps no other area of research in the connections between periodontal disease, systemic disease, and HIV has received as much attention as the role of the periodontal microbiome in the invasion of the HIV virus and activation of latent viruses. A similar phenomenon may occur in the gut as changes in the microbiota may enhance the attachment and invasion of HIV<sup>130,131</sup>. In particular, the role of one keystone periodontal pathogen, *Porphyromonas gingivalis* and its interactions with HIV has been extensively investigated in vitro. Studies have shown that *P. gingivalis* can first promote invasion of immune cells through a variety of mechanisms. One of these mechanisms is the interaction of *P. gingivalis* gingipains at the HIV gp120 domain<sup>132</sup> which can then promote internalization of the HIV into a variety of

cells<sup>133</sup>. In addition, *P. gingivalis* has been shown in vitro to increase the expression of the CCR5 receptor for HIV on oral epithelial cells<sup>134,135</sup> and may facilitate the transfer of HIV from oral epithelial cells to oral dendritic cells and other oral antigen presenting cells<sup>134</sup>. However, these effects of *P. gingivalis* in the promotion of HIV infection in vivo have yet to be determined.

With the advent of cART, while effective reductions in viral load and reconstitution of some of the immune system is a beneficial outcome, there is also a persistent residual level of systemic immune activation and inflammation that can potentially reactivate any latent pools of HIV particles. Products of bacteria in periodontal disease may both directly promote this reactivation through direct actions on cells harboring latent HIV reservoirs, or indirectly through the local and systemic effects of bacterial translocation. Direct effects of periodontal bacteria on HIV activation include evidence that the periodontal pathogens *P. gingivalis*, *F. nucleatum*, and *Treponema denticola* can enhance reactivation of HIV in infected monocytes and macrophages by binding to Toll-like receptors 2 and 9 on these cells<sup>94,136–139</sup> and by directly activating the promoter locus of HIV in these cells<sup>140–144</sup>. Similar effects in increased HIV gene transcription and activation have been observed on cultured HIV infected macrophages and dendritic cells<sup>142,143,145</sup>. Lipopolysaccharide from periodontal pathogenic bacteria can also induce HIV reactivation by a similar action on the promoter locus of HIV.<sup>146</sup>

While periodontal disease severity may decrease after cART, systemic inflammatory markers may remain<sup>147</sup> leading to persistent immune activation<sup>148</sup> and barrier dysfunction of gut mucosal tract<sup>148,149,150</sup>. This persistent immune activation seen in some HIV patients receiving cART can be enhanced by the presence of chronic translocation of bacteria and release of inflammatory mediators from inflamed periodontal tissues<sup>148</sup>. There is now a considerable body of evidence that several of these inflammatory mediators derived directly from inflamed periodontal tissues or from extraoral inflammatory responses to translocated bacteria can in turn activate latent reservoirs of HIV. For example, common elevated inflammatory mediators from periodontal diseases including interleukin-6, interleukin-8 and granulocyte-macrophage colony stimulating factor have been shown to activate HIV in monocytes, macrophages, dendritic cells, and T-cells<sup>87,137,138,151,152</sup>.

## **OTHER CONSIDERATION IN THE INCIDENCE AND PROGRESSOIN OF PERIODONTAL DISEASES AND OTHER ORAL CONDITIONS IN THE cART ERA**

While the principal focus of the effects of cART on the incidence and progression of periodontal diseases in HIV patients has been on the interactions between alterations in the microbiota and the host response, there are several other considerations that may also play a direct or indirect role for the HIV patient on cART that may also contribute to periodontal diseases and caries. These include the effects of cART on salivary flow, reduced cognitive function, effects of HIV infection and cART on bone mineralization and systemic diseases, and conditions that may adversely affect periodontal health such as diabetes. Each of these conditions or diseases share some common characteristics that increase the HIV patient's

susceptibility to periodontal diseases and are discussed below. These characteristics include an altered immune response and impaired host response to other harmful microbiota, an enhanced destructive inflammatory response, and/or impairment of periodontal tissue integrity leading to greater susceptibility to breakdown or resorption. In the following section, some examples the implications of HIV on some of these other factors and their potential role in periodontal diseases progression as well as in other dental diseases will be presented.

### **Effects of salivary hypofunction on periodontal disease**

Reduced salivary flow, with or without salivary gland enlargement, is one of the known complications of HIV infection<sup>153,154</sup>. Several studies have observed reduced salivary flow rate with HIV infection<sup>155</sup> particularly at advanced stages of the disease. In the cART era, reduced salivary flow and xerostomia is a common side effects of some cART regimens<sup>156,157</sup>. These reduced salivary flow conditions have been clearly shown to be associated with an increase in dental caries, and may also have an adverse effect on periodontal diseases. While several studies have demonstrated a strong association of cART with an increase in dental caries and periodontal diseases, the role of hyposalivation in cART treatment in periodontal disease progression merits further investigation<sup>158,159</sup>.

### **Associations and Connections between HIV, cART and Dementia**

As with non HIV infected patients, it is expected that the aging population of HIV infected patients receiving cART will experience reductions in cognitive function ranging from mild cognitive impairment to severe dementia<sup>160</sup>. Such impairments of cognitive function may have a major adverse effect on both periodontal health and caries through the reduced ability to perform routine oral hygiene. With the HIV infected patient this would be a particular problem as reduced cognitive function appears to be more severe and at earlier ages<sup>161</sup>. Recent research on these patients, has provided new insights to the interplay between HIV infection, cART therapy, periodontal diseases, and cognitive function. There is evidence that bacteria themselves, and bacterial products from inflamed periodontal tissues can enter the brain<sup>162</sup> resulting in a local inflammatory reaction and impairment of neural function. While the integrity of the protective blood brain barrier is maintained through the structural integrity of the cell to cell junctions of the barrier lining, there is evidence that both HIV and bacteria from the periodontal tissues can damage this barrier, and thereby allow the entry of these bacterial into the brain<sup>163</sup>.

### **Effects of osteoporosis on the initiation, progression and severity of periodontal diseases**

It is now well established that patients with reduced bone mineralization, particularly in the more severe forms of osteoporosis are more prone to periodontal breakdown. As populations with HIV live longer, complications associated with aging such as osteoporosis become more important considerations for the patient's overall health and health of the periodontium. In addition, both HIV infection and cART may have direct or indirect roles in the earlier initiation and greater severity of osteoporosis. For example, osteoporosis has been reported to be more prevalent in HIV patients including those under cART<sup>164-167</sup>. Furthermore, in a population of HIV infected younger men, the levels of bone mineralization were reported to be lower than their HIV uninfected counterparts<sup>168,169</sup>.

One possible underlying cause for a decrease in bone mineralization in HIV infected patients is the persistent chronic systemic immune activation observed even in those ‘successfully’ treated with cART. The elevation of inflammatory cytokines associated with systemic immune activation such as transforming growth factor-alpha, interleukin-6, interleukin-17, nuclear factor-kappa B and interleukin-1 beta<sup>151,170</sup> directly or indirectly leads to both systemic bone loss and localized alveolar bone loss. In the younger HIV infected patient, poor nutrition, and a lower adherence to the cART regimen may also contribute to the observed lower levels of bone mineralization and osteoporosis<sup>171</sup>.

## CONCLUSIONS

Over the past two decades the face of HIV infection has changed dramatically from a disease with almost certain mortality due to direct effects of the HIV and serious co-morbidities, to a manageable chronic condition with an extended lifespan through newer therapies (cART). However, many clinical and research challenges remain in addressing the nature of this disease and the interactions between different sites of HIV infection and areas of the body where HIV exerts a direct and/or indirect effect. In addition, new issues in the diagnosis, treatment and pathogenesis of an aging population infected with HIV at different stages of their lifetime will arise. This article has presented some of the most important of these epidemiological and research trends. One common theme in this presentation is the increasing importance of interactions between clinicians and researchers in the fields of periodontal diseases, other oral diseases, as well as in other systemic conditions. New and continued collaborations between these different dental, medical and basic science disciplines should yield new insights into the interactions between periodontal diseases and systemic conditions, not only for the HIV infected patient, but for non HIV infected patients with periodontal diseases and associated local and systemic diseases and conditions.

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**Figure 1.** Severe linear gingival erythema (white arrows) (from a previous *Periodontology 2000*. Will get permission from Wiley)



**Figure 2.**  
Necrotizing ulcerative periodontitis involving maxillary left lateral incisor, canine, and first premolar





**Figure 3.** Necrotizing stomatitis or ulcerative necrotizing ulcerative stomatitis on buccal aspect of mandibular left canine (need copyright permission; J Oral Pathol Med (2009) 38: 481–488)



**Figure 4.**  
Pseudomembranous candidiasis, buccal mucosa and lateral tongue



**Figure 5.**  
Single human papilloma virus wart on upper right labial mucosa



**Figure 6.**  
Multiple clustered human papilloma virus warts on upper labial mucosa